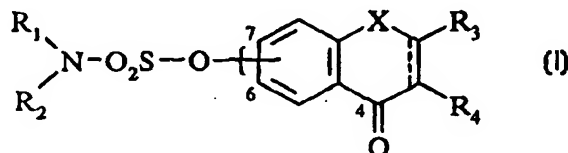




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(21) International Application Number: PCT/EP99/02349 (22) International Filing Date: 7 April 1999 (07.04.99) (30) Priority Data: 9807779.5 9 April 1998 (09.04.98) GB (71) Applicant (for all designated States except AT US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). (71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT). (72) Inventors; and (75) Inventors/Applicants (for US only): BILLICH, Andreas [DE/AT]; Dr.-Gohrengasse 24, A-2340 Mödling (AT). NUSSBAUMER, Peter [AT/AT]; Kaiserin-Elisabeth-Strasse 5/9, A-2344 Maria Enzersdorf (AT). SCHREINER, Erwin [AT/AT]; Traviatagasse 12-16/15/5, A-1230 Wien (AT). SCHUSTER, Ingeborg [AT/AT]; Dr.-Heinrich-Maierstrasse 60/5, A-1180 Wien (AT).		(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	

(54) Title: CHROMANONE AND THIOCHROMANONE DERIVATIVES



(57) Abstract

The invention concerns compounds of formula (I), wherein R₁ and R₂ independently are hydrogen, acyl, alkoxycarbonyl or alkyl; either the sulfamoyloxy side chain is bound to the 6 position; R₃ is alkyl; alkenyl; alkynyl; a cycloalkyl moiety optionally substituted by alkyl, alkoxy or halogen; arylalkyl; arylalkenyl; arylalkynyl; acyl; cycloalkylalkyl; 3-oxo-2-oxacamphanyl; 6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl; a heteroaryl moiety optionally substituted by alkyl, alkoxy or halogen; or is heteroarylalkyl; and R₄ is hydrogen; alkyl; hydroxy; or alkoxy; or the sulfamoyloxy side chain is bound to the 7 position; R₃ has the significance indicated above for R₄; and R₄ has the significance indicated above for R₃; X is O or S; and the symbol — is a single or a double bond; in free form or salt form. They can be prepared by sulfamoylation of corresponding hydroxylated compounds, by reduction and/or by N-substitution. They are indicated for use as pharmaceuticals, particularly in the prophylactic or curative treatment of illnesses responsive to steroid sulfatase inhibition.

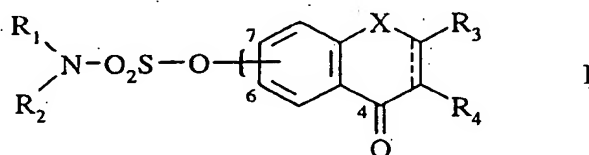
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CHROMANONE AND THIOCHROMANONE DERIVATIVES

The invention relates to chromanone and thiochromanone derivatives. It concerns the compounds of formula I



wherein

R_1 and R_2 independently are hydrogen, acyl, alkoxycarbonyl or alkyl;

either the sulfamoyloxy side chain is bound to the 6 position;

R_3 is alkyl; alkenyl; alkynyl; a cycloalkyl moiety optionally substituted by alkyl, alkoxy or halogen; arylalkyl; arylalkenyl; arylalkynyl; acyl; cycloalkylalkyl; 3-oxo-2-oxacamphanyl; 6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl; a heteroaryl moiety optionally substituted by alkyl, alkoxy or halogen; or is heteroarylalkyl; and

R_4 is hydrogen; alkyl; hydroxy; or alkoxy;

or the sulfamoyloxy side chain is bound to the 7 position;

R_3 has the significance indicated above for R_4 ; and

R_4 has the significance indicated above for R_3 ;

X is O or S; and the symbol --- is a single or a double bond;

in free form or salt form; hereinafter briefly named "the compounds of the invention".

A compound of formula I may be present in free, i.e. neutral or base, form or, where such forms exist, in salt, particularly acid addition salt form. A compound of formula I in free form may be converted into a salt form in conventional manner and vice-versa.

The sulfamoyloxy side chain is bound preferably to the 6 position.

Acyl preferably is the residue of a carboxylic acid, in particular of an alkyl, arylalkyl or aryl carboxylic acid. It preferably is alkylcarbonyl of altogether 2 to 5 carbon atoms, it especially is acetyl. Alkoxy carbonyl preferably is of altogether 2 to 5 carbon atoms, it especially is methoxycarbonyl. Alkyl as a moiety R_1 or R_2 or as part of a substituent preferably is of 1 to 5 carbon atoms, it especially is methyl. Alkyl as a moiety R_3 or R_4 preferably is of 1 to 12 carbon atoms, it especially is methyl, ethyl or t-butyl, particularly t-butyl. Alkenyl preferably is of 2 to 5 carbon atoms, it conveniently is ethenyl. Alkynyl preferably is of 2 to 5 carbon atoms, it conveniently is ethynyl.

A cycloalkyl moiety may be monocyclic or polycyclic. When it is monocyclic, it preferably is of 3 to 12 carbon atoms, it especially is cyclopropyl, cyclopentyl or cyclohexyl; when it is polycyclic, it preferably is adamantyl, especially 1-adamantyl; nor-adamantyl; or bicyclo[2.2.2]oct-1-yl. When cycloalkyl is substituted, it preferably is substituted by alkyl.

Arylalkyl preferably is of 1 to 4 carbon atoms in the alkylene part thereof. It preferably is 2-phenylethyl or benzyl. Arylalkenyl preferably is of 2 to 4 carbon atoms in the alkenylene part thereof. It preferably is 2-phenylethenyl, preferably in the trans configuration. Arylalkynyl preferably is of 2 to 4 carbon atoms in the alkynylene part thereof.

Cycloalkylalkyl preferably is of 1 to 4, especially 1 carbon atom in the alkylene part thereof. The cycloalkyl part thereof may be monocyclic or polycyclic; when it is monocyclic, it preferably is of 3 to 12 carbon atoms, it especially is cyclopentyl or cyclohexyl; when it is polycyclic, it preferably is bicyclo[2.2.1]hept-2-yl.

Heteroaryl and the heteroaryl part of heteroarylalkyl preferably is pyridyl or thienyl. It preferably is unsubstituted. The alkylene part of heteroarylalkyl preferably is of 1 to 4, especially of 1 or 2 carbon atoms.

Alkoxy preferably is of 1 to 4 carbon atoms, it especially is methoxy. Halogen is fluorine, chlorine or bromine, preferably chlorine.

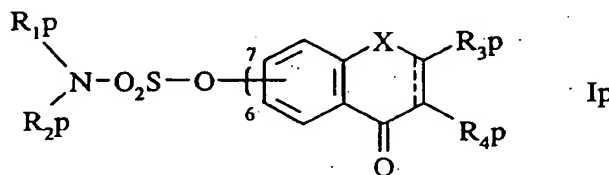
R_1 and R_2 preferably are hydrogen or alkyl, especially hydrogen. They preferably are identical. R_3 preferably is alkyl or cycloalkyl. R_4 preferably is hydrogen. X conveniently is O. The symbol \equiv preferably is a double bond.

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In a preferred subgroup of compounds of the invention R_1 and R_2 are identical and are hydrogen or methyl, and R_3 is t-butyl; cyclopentyl; cyclohexyl; adamantyl; bicyclo[2.2.1]hept-2-ylmethyl; nor-adamantyl; 4-pentylbicyclo[2.2.2]oct-1-yl; 6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl; camphanyl; styryl; 2,2,3,3-tetramethylcyclopropyl; alkyl of 1 to 4 carbon atoms; or phenylalkyl of 1 to 4 carbon atoms in the alkylene part thereof.

In a further preferred subgroup R_1 , R_2 and R_4 are hydrogen; the sulfamoyloxy side chain is bound to the 6 position; R_3 is a bulky moiety selected from the significances indicated above for R_3 , preferably branched alkyl of 4 to 12 carbon atoms, such as tert-butyl; a monocyclic cycloalkyl moiety of 5 to 12 carbon atoms or a bi- or tricyclic cycloalkyl moiety of 6 to 10 carbon atoms, each optionally mono- or independently di- or independently trisubstituted by alkyl of 1 to 5 carbon atoms; 3-oxo-2-oxacamphanyl; or 6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl; and X and the symbol --- are as defined above.

A further preferred subgroup of compounds of the invention is the compounds of formula Ip



wherein

R_{1p} and R_{2p} independently are hydrogen or alkyl;

either the sulfamoyloxy side chain is bound to the 6 position,

R_{3p} with the exception of 3-oxo-2-oxacamphanyl has the significance indicated above for R_3 ,
and

R_{4p} is hydrogen;

or the sulfamoyloxy side chain is bound to the 7 position,

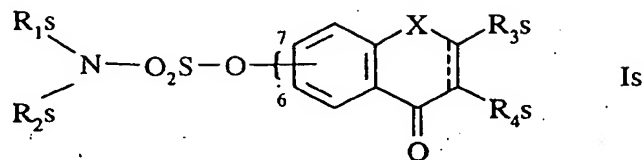
R_{3p} is hydrogen, and

R_{4p} with the exception of 3-oxo-2-oxacamphanyl has the significance indicated above for R_3 ;
and

X and the symbol --- are as defined above;

in free form or salt form.

A further preferred subgroup of compounds of the invention is the compounds of formula Is



wherein

R_{1s} is hydrogen, methyl, acetyl or methoxycarbonyl;

R_{2s} is hydrogen or methyl;

either the sulfamoyloxy side chain is bound to the 6 position,

R_{3s} is alkyl of 1 to 12 carbon atoms; a monocyclic cycloalkyl moiety of 3 to 12 carbon atoms optionally substituted by methyl; 1-adamantyl; nor-adamantyl;

4-pentylbicyclo[2.2.2]oct-1-yl; phenylalkyl of 7 to 9 carbon atoms; 2-phenylethenyl;

bicyclo[2.2.1]hept-2-ylmethyl; 3-oxo-2-oxacamphanyl; or

6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl, and

R_{4s} is hydrogen;

or the sulfamoyloxy side chain is bound to the 7 position,

R_{3s} is hydrogen, and

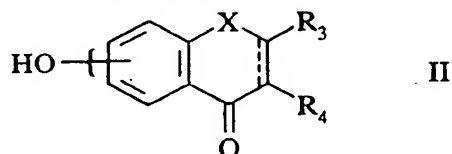
R_{4s} is cycloalkyl of 5 to 7 carbon atoms; and

X and the symbol --- are as defined above;

in free form or salt form.

The invention also provides a process for the preparation of the compounds of the invention comprising

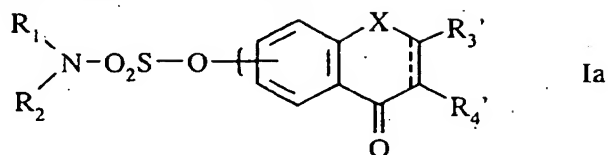
a) sulfamoylating the compounds of formula II



wherein R_3 , R_4 , X and the symbol --- are as defined above; or

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- b) for the preparation of the compounds of formula Ia



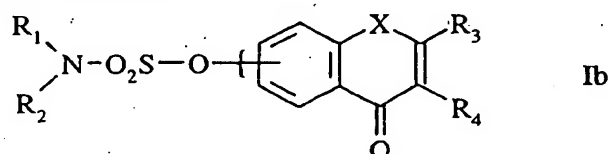
wherein X, R₁, R₂ and the symbol --- are as defined above and

R₃' and R₄' with the exception of alkenyl, alkynyl, arylalkenyl, arylalkynyl and

6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl have the significance indicated above

for, respectively, R₃ and R₄,

reducing the corresponding compounds of formula Ib



wherein the substituents are as defined above; or

- c) for the preparation of the compounds of formula I wherein at least one of R₁ and R₂ is alkyl, acyl or alkoxycarbonyl,

N-substituting the compounds of formula I wherein at least one of the substituents R₁ and R₂ is hydrogen;

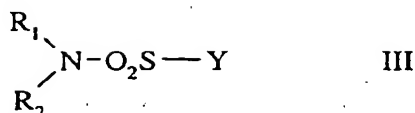
and recovering the resultant compounds of formula I in free form or salt form.

The process of the invention is carried out in conventional manner.

Process variant a) is performed using standard conditions for sulfamoylation, e.g. by reacting a compound of formula II with:

- α) sulfonyl chloride and sodium- or potassium azide to generate corresponding intermediates wherein the hydrogen atom of the hydroxy group is replaced with a group -SO₂N₃, which after reduction of the azide group give compounds of formula I wherein R₁ and R₂ are hydrogen, or
- β) ClSO₂-NCO, followed by aqueous hydrolysis of the resultant intermediates to yield compounds of formula I wherein R₁ and R₂ are hydrogen, or

γ) a compound of formula III



wherein R_1 and R_2 are as defined above and Y is a leaving group, e.g. halogen, preferably chlorine, in an inert solvent, e.g. dimethylformamide, where convenient with addition of an organic base, such as an organic tertiary amine, or an inorganic base, e.g. an alkali(hydrogen)carbonate or alkali hydride, preferably sodium hydride.

Process variant b) may be performed following standard procedures for hydrogenation of double bonds, e.g. catalytically, preferably using hydrogen in combination with a hydrogenation catalyst such as Pd, Pt or Rh, most preferably Pd on charcoal. Starting from compounds of formula I wherein R_3 is alkenyl, alkynyl, arylalkenyl or arylalkynyl, in a first step of the reaction these groups are reduced. The reaction may be stopped at this stage and the double bond in the chromenone ring remain unchanged. Further reduction gives compounds of formula Ia wherein the symbol $---$ is a single bond.

Process variant c) is performed according to standard procedures for N-substitution by alkylation or acylation, conveniently using alkylhalogenides, -sulfates or -mesylates, preferably alkyl iodides, or acyl- or alkoxycarbonylhalides, preferably chlorides, preferably in the presence of a suitable base, such as an alkali carbonate or alkali hydride, conveniently in an inert and preferably polar solvent such as acetone or dimethylformamide, preferably at temperatures of between about -20° and about 120°C , preferably between room temperature and about 60°C .

The resultant compounds of the invention may be recovered from the reaction mixture and isolated and purified in conventional manner. Isomers, such as enantiomers, may be obtained in conventional manner, e.g. by fractional crystallization or asymmetric synthesis from corresponding asymmetrically substituted, e.g. optically active starting materials.

The starting materials and intermediate compounds are either known or can be prepared according to known methods or analogously as described in the Examples.

The following Examples illustrate the invention. All temperatures are in degrees Celsius. The compounds of the invention are in free form unless specified otherwise. The following abbreviations are used:




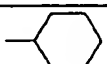



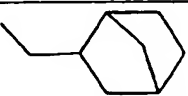
Ad = 1-adamantyl = tricyclo[3.3.1.1^{3,7}]dec-1-yl
Cam = 1-camphanyl = 4,7,7-trimethylbicyclo[2.2.1]hept-1-yl
db = double bond
DMSO = dimethylsulfoxide
mp = melting point
nor-Ad = noradamantyl
sb = single bond
t- = tertiary

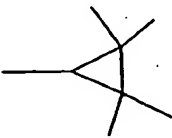
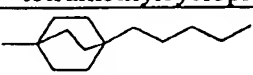
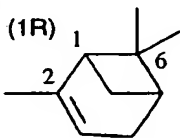

Example 1: 2-t-Butyl-4H-chromen-4-one-6-O-sulfamate

[process variant a)]

158 mg sodium hydride (80 % in mineral oil) is added to a solution of 400 mg **2-t-butyl-6-hydroxy-4H-chromen-4-one** in dry dimethylformamide. After stirring for 30 minutes at room temperature 630 mg **amidosulfonyl chloride** is added, and stirring is continued for additionally 3 hours. The solvent is distilled off in vacuo and the residue partitioned between water and ethyl acetate. The aqueous layer is extracted with ethyl acetate, and the organic layers are combined, dried over magnesium sulfate and concentrated in vacuo. The residue is taken up in dichloromethane and passed through a short silica gel column (cyclohexane/ethyl acetate 1/1). The **title compound** is obtained (colourless crystals; mp 178-180°- from 2-propanol; mp 180°- from toluene).

Analogously as described in Example 1 the following compounds of the invention are prepared:

Example No.	Position of sulfa-moyloxy moiety	R ₁	R ₂	R ₃	R ₄	X	---	mp
2	6	H	H		H	O	db	158-160°
3	6	H	H		H	O	sb	127°
4	6	H	H		H	O	db	170-171°
5	6	H	H		H	O	sb	136-138°
6	6	H	H	---CH=CH--  (E)	H	O	db	185-188°
7	6	H	H	$\text{---C(CH}_3)_3$	H	O	sb	118-120°
8	6	H	H	$\text{---CH}_2\text{CH}_2\text{---}$ 	H	O	db	155-158°
9	6	H	H	Ad	H	O	db	166-168°
10	6	CH ₃	CH ₃	$\text{---C(CH}_3)_3$	H	O	db	83-85°
11	6	H	H	$\text{---CH}_2\text{---}$ 	H	O	db	157-160°
12	6	H	H	$\text{---(CH}_2)_8\text{---CH}_3$	H	O	db	77-80°
13	6	H	H	(+)-3-oxo-2-oxa-Cam	H	O	db	210-212°
14	6	H	H	(-)-3-oxo-2-oxa-Cam	H	O	db	213-215°
15	6	H	H	Ad	H	O	sb	192-194°
16	6	H	H	 bicyclo- [2.2.1]hept-2-ylmethyl	H	O	db	165°


Example No.	Position of sulfa-moyloxy moiety	R ₁	R ₂	R ₃	R ₄	X	---	mp
17	6	H	H	nor-Ad	H	O	db	165-167°
18	6	H	H	nor-Ad	H	O	sb	165-167°
19	6	H	H	 2,2,3,3-tetramethylcyclopropyl	H	O	db	148°
20	6	H	H	 4-pentylbicyclo[2.2.2]-oct-1-yl	H	O	db	185°
21	6	H	H	-CH ₂ CH ₂ CH ₃	H	O	db	148°
22	6	H	H	 (1R)(-)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl	H	O	db	112°
23	6	H	H	-C(CH ₃) ₃	H	S	db	150-153°
24	6	H	H	Ad	H	S	db	220°
25	7	H	H	H		O	db	160-163°
26	6	H	H	cyclododecyl	H	O	db	168-170°
26a	6	H	H	1,1-dimethylnon-1-yl	H	O	db	122°

Example 27: 2-Cyclohexylchromen-4-on-6-O-sulfamate

(process variant b)

90 mg 2-cyclohexyl-4H-chromen-4-on-6-O-sulfamate (Example 4) is dissolved in ethyl acetate and hydrogenated over palladium (10 % on charcoal) at atmospheric pressure and room temperature for 3 hours. The mixture is filtered over silicagel (celite), and the filtrate is evaporated in vacuo. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 2/1). The title compound is obtained (colourless crystals; mp 136-138°).

Analogously as described in Example 27 the following compounds of the invention are obtained:

Example No.	Position of sulfamoyloxy moiety	R ₁	R ₂	R ₃	R ₄	X	---	mp
28	6	H	H		H	O	sb	127°
29	6	H	H	-C(CH ₃) ₃	H	O	sb	118-120°
30	6	H	H	Ad	H	O	sb	192-194°
31	6	H	H	nor-Ad	H	O	sb	165-167°

Example 32: N-Acetylsulfamic acid 2-(1-adamantyl)-4H-chromen-4-on-6-yl ester

(process variant c)

100 mg 2-(1-adamantyl)-4H-chromen-4-one-6-O-sulfamate (Example 9) and 32 mg of triethylamine are dissolved in dry dichloromethane and treated with 32 mg of acetic anhydride at room temperature. The mixture is stirred 1 hour at room temperature, then poured into aqueous pH 7 buffer solution and extracted with ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo. The title compound is obtained (viscous gum).

[¹H-NMR (DMSO-d₆): 7.71 (d, J = 2.8Hz, 1H); 7.59 (d, J = 9Hz, 1H); 7.51 (dd, J = 2.8 + 9Hz, 1H); 6.10 (s, 1H); 5.77 (s, 1H); 2.06 (br.s, 3H); 1.93 (br.s, 6H); 1.73 (br.s, 6H); 1.69 (s, 3H)].

Example 33: N,N-Dimethylsulfamic acid 2-t-butyl-4H-chromen-4-on-6-yl ester

(process variant c)

52 mg sodium hydride (95%) is added to a solution of 240 mg **2-t-butyl-4H-chromen-4-one-6-O-sulfamate** (Example 1) in dry dimethylformamide. The mixture is stirred for 20 minutes at room temperature and then treated with 200 mg of **methyl iodide**. Stirring is continued for an additional 2 hours, the mixture is poured into aqueous pH 7 buffer solution and extracted with ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 5/1). The **title compound** is obtained (colourless crystals; mp 83 - 85°).

Analogously as described in Examples 32 and 33 the following compound of the invention is obtained:

Example No.	Position of sulfa-moyloxy moiety	R ₁	R ₂	R ₃	R ₄	X	==	mp
34	6	-COOCH ₃	H	Ad	H	O	db	amorphous*

* ¹H-NMR (DMSO-d₆): 7.75 (d, J = 2.7Hz, 1H); 7.63 (d, J = 9Hz, 1H); 7.57 (dd, J = 2.7 + 9Hz, 1H); 6.12 (s, 1H); 3.38 (s, 3H); 2.09 (br.s, 3H); 1.96 (s, 3H); 1.95 (s, 3H); 1.75 (br.s, 3H).

The starting materials can be prepared in the following manner:

A) 6-Hydroxy-2-(2-methylphenyl)-4H-chromen-4-one

6-Benzyloxy-2-(2-methylphenyl)-4H-chromen-4-one (mp 115°) is hydrogenated in ethyl acetate over palladium (10 % on charcoal) at atmospheric pressure and room temperature for 1 hour. The mixture is filtered over celite, and the filtrate is evaporated in vacuo. The **title compound** is obtained (colourless crystals; mp 180°).

B) 2-(1-Adamantyl)-6-hydroxy-4H-chromen-4-one

a) 4 g 1-adamantoyl chloride are added to a solution of 1.5 g 2,5-dihydroxyacetophenone in dry pyridine. The mixture is stirred for 18 hours at 40°, poured into water and extracted with ethyl acetate. The combined organic layers are washed 3 times with 1 N aqueous hydrochloric acid and subsequently with aqueous sodium carbonate solution, dried over magnesium sulfate and concentrated in vacuo. The crude product is dissolved in dry dimethylformamide and added dropwise at 5° to a suspension of 330 mg of sodium hydride (80 % in mineral oil) in dry dimethylformamide. The cooling bath is removed, and the mixture is stirred for 4 hours at room temperature. Then 1.5 ml of acetic acid and 250 ml of water are added, followed by extraction with ethyl acetate. The combined extracts are dried over magnesium sulfate and evaporated in vacuo. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 6/1) to remove starting materials and major by-products. Cyclisation of the resultant 1-[5-(1-adamantoyloxy)-2-hydroxyphenyl]-3-(1-adamantyl)-1,3-propandione is achieved by treatment with 20 ml of 32 % aqueous hydrochloric acid in methanol/dioxane. 6-(1-adamantoyloxy)-2-(1-adamantyl)-4H-chromen-4-one is obtained:

¹H-NMR (CDCl₃): 7.81 (d, J = 2.7 Hz, 1H), 7.48 (d, J = 9 Hz, 1H), 7.35 (dd, J = 2.7 + 9 Hz, 1H), 6.19 (s, 1H), 2.12 (br.s, 12H), 1.97 (s, 3H), 1.95 (s, 3H), 1.78 (s, 12H).

b) 330 mg 6-(1-adamantoyloxy)-2-(1-adamantyl)-4H-chromen-4-one is dissolved in dioxane and treated with 5 ml of 10 % aqueous potassium hydroxide solution. The mixture is stirred for 3 hours at room temperature and then poured into 2M aqueous pH 7 buffer solution. Extraction with ethyl acetate yields after drying and evaporation a crude product which is purified by chromatography. The **title compound** is obtained [colourless crystals; mp 230° (from 2-propanol)].

Analogously the following compounds can be prepared:

6-Hydroxy-2-(2-phenylethenyl)-4H-chromen-4-one (mp 217-222°);

2-t-butyl-6-hydroxy-4H-chromen-4-one (mp 169-171°);

2-benzyl-6-hydroxy-4H-chromen-4-one

[¹H-NMR (CDCl₃): 9.10 (br.s, 1H), 7.50 (d, J = 2.9 Hz, 1H), 7.20 - 7.35 (m, 6H), 7.18 (dd, J = 2.9 + 9 Hz, 1H), 6.03 (s, 1H), 3.91 (s, 2H)];

(+)-6-hydroxy-2-(4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]hept-1-yl)-4H-chromen-4-one
(mp 227°);

2-nonyl-6-hydroxy-4H-chromen-4-one (mp 95-97°);

(-)-6-hydroxy-2-(4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]hept-1-yl)-4H-chromen-4-one
(mp 232°);

2-(bicyclo[2.2.1]hept-2-ylmethyl)-6-hydroxy-4H-chromen-4-one (mp 186°);

6-hydroxy-2-noradamantyl-4H-chromen-4-one (mp 190°);

6-hydroxy-2-(2,2,3,3-tetramethylcyclopropyl)-4H-chromen-4-one (mp 173°);

6-hydroxy-2-(4-pentylbicyclo[2.2.1]oct-1-yl)-4H-chromen-4-one (mp 180-182°);

6-hydroxy-2-propyl-4H-chromen-4-one (mp 150°);

2-((1R)-(-)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)-6-hydroxy-4H-chromen-4-one
(mp 155-158°);

2-cyclododecyl-6-hydroxy-4H-chromen-4-one (mp 168-170°);

2-cyclohexyl-6-hydroxy-4H-chromen-4-one

[¹H-NMR (DMSO-d₆): 10.72 (br.s, 1H); 7.98 (s, 1H); 7.89 (d, J = 8.7Hz, 1H); 6.89 (dd, J = 2.2 + 8.7Hz, 1H), 6.79 (d, J = 2.2Hz, 1H); 2.58 - 2.70 (m, 1H); 1.65 - 1.80 (m, 5H); 1.20 - 1.35 (m, 5H)];

2-(1,1-dimethylnon-1-yl)-6-hydroxy-4H-chromen-4-one.

C) 2-(1-Adamantyl)-6-hydroxy-4H-thiochromen-4-one

a) 1.4 g 4-methoxythiophenol is added to 10 g of polyphosphoric acid preheated to about 90°.

Then 2.5 g ethyl 3-(1-adamantyl)-3-oxopropionate is added slowly, and the mixture is stirred for altogether 1.5 hours at 90°. The mixture is poured onto ice/water, vigorously stirred and extracted with ethyl acetate. The combined organic layers are dried over magnesium sulfate and evaporated in vacuo. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 6/1).

2-(1-adamantyl)-6-methoxy-4H-thiochromen-4-one is obtained (colourless crystals; mp 140°).

b) Under argon 14 ml of 1M boron tribromide solution in dichloromethane are added at room temperature to a solution of 1.12 g 2-(1-adamantyl)-6-methoxy-4H-thiochromen-4-one in dry dichloromethane. After stirring for 1 hour the mixture is poured onto ice/water and extracted with dichloromethane. The combined organic layers are washed with aqueous sodium bicarbonate solution, dried over magnesium sulfate and evaporated in vacuo. The title compound is obtained (colourless crystals; mp 257° after chromatography on silica gel using cyclohexane/ethyl acetate 4/1 as an eluant).

Analogously the following compound can be prepared:

2-t-Butyl-6-hydroxy-4H-thiochromen-4-one (mp 188-190°).

The compounds of formula I in free form or pharmaceutically acceptable salt form, hereinafter briefly named "the agents of the invention", possess pharmaceutical activity. They are indicated for use as pharmaceuticals. In particular, they inhibit steroid sulfatase activity.

Steroidal hormones in particular tissues are associated with several diseases, such as tumors of the breast, endometrium and prostate. Important precursors for the local production of these steroid hormones are steroid 3-O-sulfates which are desulfated by the enzyme steroid sulfatase in the target tissues. Inhibition of this enzyme results in therapeutically relevant, reduced local levels of the corresponding active steroidal hormones. Furthermore, steroid sulfatase inhibitors may also be immunosuppressive, and enhance memory when delivered to the brain.

Further, it has now been found that the agents of the invention reduce endogenous levels of androgens and/or estrogens in skin and are thus particularly indicated for use in the treatment of androgen-dependent disorders of the pilosebaceous unit, such as acne, seborrhea, androgenic alopecia and hirsutism, and in the topical treatment of squamous cell carcinoma. Acne is a polyetiological disease caused by interplay of numerous factors, such as inheritance, sebum, hormones, and bacteria. The most important causative factor in acne is sebum production; in almost all acne patients sebaceous glands are larger and produce more sebum than in persons with healthy skin. The development of the sebaceous gland and the extent of sebum production is controlled hormonally by androgens, which play a crucial role in the pathogenesis of acne as well as seborrhea, which is also related to androgen-dependent sebum formation and is important both in initiation and development of acne. Androgenic alopecia is caused by an increased number of hair follicles in the scalp entering the telogen phase and by increased duration of the telogen phase. It is a genetically determined hair loss mediated by androgens in the target tissue. Hirsutism is a pathological thickening and strengthening of hair which is characterized by a masculine pattern of hair growth in children and women. Hirsutism is androgen-induced, either by increased formation of androgens or by increased sensitivity of the hair follicle to androgens.

The agents of the invention are therefore indicated for use as steroid sulfatase inhibitors, particularly in the prevention and treatment of illnesses responsive to steroid sulfatase inhibition, such as illnesses in which the steroid products of sulfatase cleavage play a role, in particular in the prevention and treatment of the following specific conditions:

androgen-dependent disorders of the pilosebaceous unit such as acne, seborrhea, androgenic alopecia and hirsutism; cancer, especially estrogen- and androgen-dependent tumors such as tumors of the breast, endometrium and prostate, and squamous cell carcinoma; inflammatory and autoimmune diseases such as rheumatoid arthritis, type I and II diabetes, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, thyroiditis, vasculitis, ulcerative colitis and Crohn's disease; skin disorders such as psoriasis, eczema and contact dermatitis; graft versus host disease; asthma; organ rejection following transplantation; and for enhancement of cognitive function, as in senile dementia, including Alzheimer's disease.

The above activities can be shown e.g. in the following assays (all temperatures are in degrees Celsius):

1. Steroid sulfatase inhibition in vitro:

a) **Purification of human steroid sulfatase:** Human placenta is obtained fresh after delivery and stripped of membranes and connective tissues. For storage the material is frozen at -70° . After thawing, all further steps are carried out at 4° , while pH values are adjusted at 20° . 400 g of tissue are homogenized in 1.2 l of buffer A (50 mM Tris-HCl, pH 7.4; 0.25M sucrose). The homogenate is centrifuged at 10'000 g for 45 minutes. The supernatant is set aside and the pellet re-homogenized in 500 ml of buffer A. After centrifugation the two supernatants are combined and subjected to ultracentrifugation (100'000 g, 1 hour). The pellet is resuspended in buffer A and the centrifugation repeated. The pellet is suspended in 50 ml of 50 mM Tris-HCl, pH 7.4 and stored at -20° until further work-up.

After thawing, microsomes are collected by ultracentrifugation as described above and suspended in 50 ml of buffer B (10 mM Tris-HCl, pH 7.0; 1 mM EDTA; 2 mM 2-mercaptoethanol; 1 % Triton X-100 v/v; 0.1 % aprotinin v/v). After 1 hour on ice with gentle agitation the suspension is centrifuged (100'000 g, 1 hour). The supernatant containing the enzyme activity is collected and the pH adjusted to 8.0 with 1M Tris.

Then the solution is applied to a hydroxyapatite column (2.6 x 20 cm) equilibrated with buffer B, pH 8.0. The column is washed with buffer B at a flow rate of 2 ml/min. The activity is recovered in the flow-through. The pool is adjusted to pH 7.4 and subjected to

chromatography on a concanavalin-A sepharose column (1.6 x 10 cm) equilibrated in **buffer C** (20 mM Tris-HCl, pH 7.4; 0.1 % Triton X-100 v/v; 0.5 M NaCl). The column is washed with **buffer C** and then the bound protein eluted with 10 % v/v methyl mannoside in **buffer C**.

Active fractions are pooled and dialysed against **buffer D** (20 mM Tris-HCl, pH 8.0; 1 mM EDTA; 0.1 % Triton X-100 v/v; 10 % glycerol v/v).

The active fractions are applied to a blue sepharose column (0.8 x 10 cm) equilibrated with **buffer D**; the column is washed and then eluted with a linear gradient of **buffer D** to 2M NaCl in **buffer D**. Active fractions are pooled, concentrated as required (Centricon 10), dialysed against **buffer D** and stored in aliquots at -20°.

b) **Assay**: Purified human steroid sulfatase also readily cleaves aryl sulfates such as 4-methylumbelliferyl sulfate. Assay mixtures are prepared by consecutively dispensing the following solutions into the wells of white microtiter plates:

- 1) 50 µl of substrate solution (1.5 mM 4-methylumbelliferyl sulfate in 0.1 M Tris-HCl, pH 7.5) (final concentration 0.5 mM);
- 2) 50 µl of diluted test compound solution diluted in 0.1 M Tris-HCl, pH 7.5, 0.1 % Triton X-100 v/v (stock solutions of the test compounds are prepared in dimethylsulfoxide; final concentrations of the solvent in the assay mixture do not exceed 1 %);
- 3) 50 µl of enzyme solution (approximately 12 U/ml) (one enzyme unit U is the amount of steroid sulfatase that hydrolyses 1 nmol of 4-methylumbelliferyl sulfate per hour at an initial substrate concentration of 500 µM in 0.1M Tris-HCl, pH 7.5; 0.1 % Triton X-100 v/v; at 37°).

Plates are incubated at 37° for 1 hour. The reaction is then stopped by addition of 100 µl of 0.2M NaOH. Fluorescence intensity is measured (Titertek Fluoroskan II) with $\lambda_{ex} = 355$ nm and $\lambda_{em} = 460$ nm.

c) **Computation of relative IC₅₀ values**: From the fluorescence intensity (I) obtained at different concentrations (c) of test compound the concentration inhibiting the enzymatic activity by 50 % (IC₅₀) is calculated using the relation

$$I = \frac{I_{100}}{1 + (c / IC_{50})^s}$$

where I_{100} is the intensity observed in the absence of inhibitor and s is the slope factor.

Estrone-3-O-sulfamate serves as reference compound and its IC_{50} value is determined in parallel to the test compounds and is about 60 nM. Relative IC_{50} values (rel IC_{50}) are defined as follows:

$$\text{rel } IC_{50} = \frac{IC_{50} \text{ of test compound}}{IC_{50} \text{ of estrone sulfamate}}$$

The agents of the invention inhibit steroid sulfatase in this assay with rel IC_{50} values in the range of 0.006 to 30.

2. Steroid sulfatase inhibition in cell extracts:

Human keratinocytes (HaCaT) or human skin-derived fibroblasts (1BR3GN) are grown to confluency using standard cell culture techniques. Cells are harvested by trypsinization, washed once with phosphate-buffered saline (PBS) and suspended in 20 mM Tris-HCl, pH 8.0. The suspension is sonicated and then centrifuged at 12000 g for 30 minutes. The supernatant is subjected to ultracentrifugation at 100000 g for 60 minutes. The resulting microsomal pellet is resuspended in buffer containing 0.1 % Triton X-100 v/v and left standing for 30 minutes. After additional centrifugation at 100000 g for 30 minutes the supernatant which contains the solubilized enzyme is removed and stored at 4°.

For assay of the enzymatic activity 10 µl of enzyme solution are added to 100 µl of 50 µM dehydroepiandrosterone sulfate (DHEAS) containing approximately 60000 dpm [3H]-DHEAS (21 Ci/mmol) in 0.1 M Tris-HCl, pH 7.5; 0.1 % v/v Triton X-100. Test compound is included at various concentrations added from stock solutions in DMSO. After incubation for 30 minutes at 37 °, 250 µl of 1N NaOH are added. The mixture is extracted with 1 ml of toluene. 800 µl of the organic layer are subjected to liquid scintillation counting to determine the fraction of substrate that has been cleaved to dehydroepiandrosterone (DHEA). IC_{50} values are computed as described above. The IC_{50} of estrone sulfamate for steroid sulfatase inhibition is in the range of about 1 - 5 nM, depending on the enzyme concentration used.

The agents of the invention inhibit steroid sulfatase activity in HaCaT keratinocytes and 1BR3GN fibroblasts with rel IC_{50} values in the range of 0.006 to 50.

3. Steroid sulfatase inhibition in HaCaT cells incubated with DHEAS:

HaCaT keratinocytes are cultivated in Dulbecco's modification of Eagle's medium (DMEM) supplemented with 10 % v/v fetal calf serum (FCS). They are grown to confluency and then harvested by trypsinization. Approximately 2×10^6 cells are dispensed into 9.6 cm^2 dishes and incubated in medium containing FCS until confluency is reached. Then the medium is changed to serum-free DMEM (1.5 ml per well); $0.3 \text{ }\mu\text{M}$ DHEAS is included as substrate with $1.5 \text{ }\mu\text{Ci/well}$ [^3H]-DHEAS (21 Ci/mmol) as tracer. Incubation is continued for 96 hours. Test compound is added from stock solutions in ethanol; the final ethanol concentration in the assay does not exceed 1 % v/v. In parallel, DHEAS is also incubated with medium without cells as a control for non-enzymatic hydrolysis. After incubation, the supernatant is removed and 1 ml is extracted with 4 ml of toluene. 3 ml of the organic layer are collected and the solvent evaporated in vacuo. The residue is taken up in acetonitrile. $10 \text{ }\mu\text{g}$ DHEA is included as carrier. The extract is analysed by high performance liquid chromatography (HPLC) using a RP C-8 column and isocratic elution with 10 mM ammonium sulfate pH 6 / acetonitrile (60/40), at a flow rate of 1 ml/min. The amount of DHEA cleaved during incubation is calculated from the area of the corresponding radioactive peak determined by continuous monitoring with a radiodetector equipped with a flow-cell. From the data obtained at various concentrations of test compound, IC_{50} and rel IC_{50} values are calculated as described above for assay 1. The IC_{50} value for estrone sulfamate is approximately 0.1 nM.

The agents of the invention show rel IC_{50} values in this assay in the range of 0.1 to 100.

For the above uses the dosage to be used will vary, of course, depending e.g. on the particular agent employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the agents are administered at a daily dosage of from about 0.1 mg/kg to about 100 mg/kg animal body weight, suitably given in divided doses two to four times daily. For most large mammals the total daily dosage is from about 5 mg to about 5000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Unit dosage forms comprise, for example, from about 1.25 mg to about 2500 mg of the compounds in admixture with at least one solid or liquid pharmaceutically acceptable carrier or diluent.

The agents of the invention may be administered in similar manner to known standards for use in such indications. The agents may be admixed with conventional chemotherapeutically acceptable carriers and diluents and, optionally, further excipients, and administered e.g. orally in such forms as tablets and capsules.

Alternatively, the agents may be administered topically in such conventional forms as lotions, solutions, ointments and creams, parenterally or intravenously. The concentration of active substance will, of course, vary depending e.g. on the particular agent employed, the treatment desired and the nature of the form. In general, however, satisfactory results are obtained in e.g. topical application forms at concentrations of from about 0.05 % to about 5 %, particularly from about 0.1 % to about 1 % by weight.

Pharmaceutical compositions comprising an agent of the invention together with at least one pharmaceutically acceptable carrier or diluent also form part of the invention, as well as a process for the preparation thereof by mixing an agent of the invention together with at least one pharmaceutically acceptable carrier or diluent. The invention also comprises the agents of the invention for use as pharmaceuticals, especially as steroid sulfatase inhibitors, particularly in the prevention or treatment of illnesses responsive to steroid sulfatase inhibition, such as illnesses in which the steroid products of sulfatase cleavage play a role, in particular in the prevention and treatment of the specific conditions indicated above. It further comprises the agents of the invention for use in the preparation of a medicament for use as steroid sulfatase inhibitor.

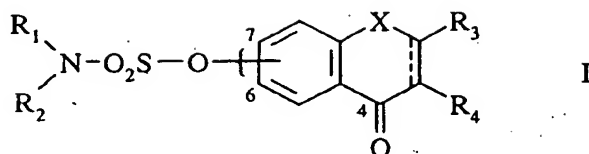
The invention particularly includes the agents of the invention for use in the treatment of androgen-dependent disorders of the pilosebaceous unit, such as acne, seborrhea, androgenic alopecia and hirsutism, or in the topical treatment of squamous cell carcinoma, as well as the agents of the invention for use in the preparation of a medicament for use in the treatment of androgen-dependent disorders of the pilosebaceous unit or in the topical treatment of squamous cell carcinoma.

The invention further concerns a method for the prophylactic or curative treatment of illnesses responsive to steroid sulfatase inhibition, such as illnesses in which the steroid products of sulfatase cleavage play a role, in particular in the prevention and treatment of the specific conditions indicated above, which comprises administering a therapeutically effective amount of an agent of the invention to a subject in need of such treatment.

The compounds of Example 1, **2-t-butyl-4H-chromen-4-one-6-O-sulfamate**, of Example 9, **2-(1-adamantyl)-4H-chromen-4-one-6-O-sulfamate**, and of Example 24, **2-(1-adamantyl)-4H-thiochromen-4-one-6-O-sulfamate**, especially the compound of Example 1, are the most preferred agents of the invention in these indications. It has, for example, been determined that in the above assay 1. these agents have a rel IC₅₀ value of about 0.4, 0.1 and 0.0064, respectively.

Claims:

1. A compound of formula I



wherein

R_1 and R_2 independently are hydrogen, acyl, alkoxycarbonyl or alkyl;

either the sulfamoyloxy side chain is bound to the 6 position;

R_3 is alkyl; alkenyl; alkynyl; a cycloalkyl moiety optionally substituted by alkyl, alkoxy or halogen; arylalkyl; arylalkenyl; arylalkynyl; acyl; cycloalkylalkyl; 3-oxo-2-oxacamphanyl; 6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl; a heteroaryl moiety optionally substituted by alkyl, alkoxy or halogen; or is heteroarylalkyl; and

R_4 is hydrogen; alkyl; hydroxy; or alkoxy;

or the sulfamoyloxy side chain is bound to the 7 position;

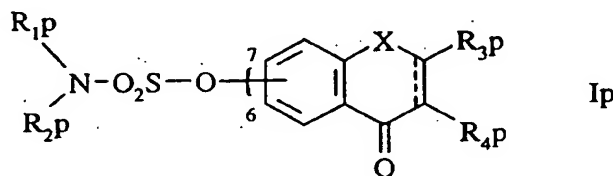
R_3 has the significance indicated above for R_4 ; and

R_4 has the significance indicated above for R_3 ;

X is O or S; and the symbol --- is a single or a double bond;

in free form or salt form.

2. A compound according to claim 1 of formula Ip



wherein

R_{1p} and R_{2p} independently are hydrogen or alkyl;

either the sulfamoyloxy side chain is bound to the 6 position,

R_{3p} with the exception of 3-oxo-2-oxacamphanyl has the significance indicated in claim 1 for R_3 , and

-22-

R_{4p} is hydrogen;

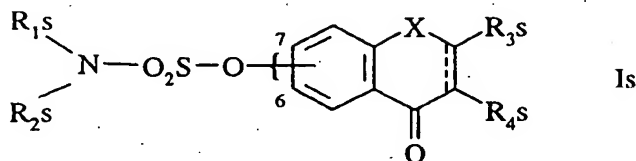
or the sulfamoyloxy side chain is bound to the 7 position,

R_{3p} is hydrogen, and

R_{4p} with the exception of 3-oxo-2-oxacamphanyl has the significance indicated in claim 1 for R_3 ; and

X and the symbol --- are as defined in claim 1;
in free form or salt form.

3. A compound according to claim 1 of formula Is



wherein

R_{1s} is hydrogen, methyl, acetyl or methoxycarbonyl;

R_{2s} is hydrogen or methyl;

either the sulfamoyloxy side chain is bound to the 6 position,

R_{3s} is alkyl of 1 to 12 carbon atoms; a monocyclic cycloalkyl moiety of 3 to 12 carbon atoms optionally substituted by methyl; 1-adamantyl; nor-adamantyl;

4-pentylbicyclo[2.2.2]oct-1-yl; phenylalkyl of 7 to 9 carbon atoms; 2-phenylethenyl;

bicyclo[2.2.1]hept-2-ylmethyl; 3-oxo-2-oxacamphanyl; or

6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl, and

R_{4s} is hydrogen;

or the sulfamoyloxy side chain is bound to the 7 position,

R_{3s} is hydrogen, and

R_{4s} is cycloalkyl of 5 to 7 carbon atoms; and

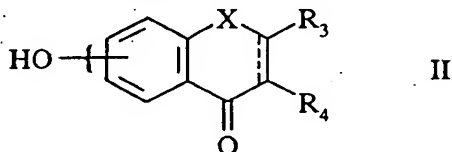
X and the symbol --- are as defined in claim 1;
in free form or salt form.

4. 2-t-butyl-4H-chromen-4-one-6-O-sulfamate in free form or salt form.

5. 2-(1-adamantyl)-4H-chromen-4-one-6-O-sulfamate or 2-(1-adamantyl)-4H-thiochromen-4-one-6-O-sulfamate, in free form or salt form.

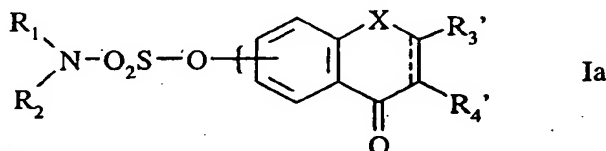
6. A process for the preparation of a compound according to claim 1 comprising

a) sulfamoylating a compound of formula II



wherein R_3 , R_4 , X and the symbol --- are as defined in claim 1; or

b) for the preparation of a compound of formula Ia



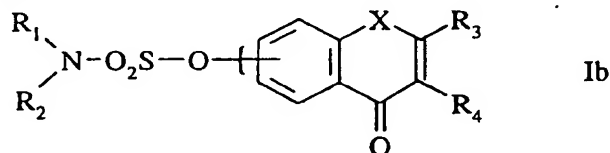
wherein X, R_1 , R_2 and the symbol --- are as defined in claim 1 and

R_3' and R_4' with the exception of alkenyl, alkynyl, arylalkenyl, arylalkynyl and

6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl have the significance indicated

in claim 1 for, respectively, R_3 and R_4 ,

reducing a corresponding compound of formula Ib



wherein the substituents are as defined in claim 1; or

c) for the preparation of a compound of formula I as defined in claim 1 and wherein at least one of R_1 and R_2 is alkyl, acyl or alkoxycarbonyl,

N-substituting a compound of formula I wherein at least one of the substituents R_1 and R_2 is hydrogen;

and recovering the resultant compound of formula I in free form or salt form.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5 in free form or pharmaceutically acceptable salt form together with at least one pharmaceutically acceptable carrier or diluent.
8. A compound according to any one of claims 1 to 5 in free form or pharmaceutically acceptable salt form, for use as a pharmaceutical.
9. A compound according to any one of claims 1 to 5 in free form or pharmaceutically acceptable salt form, for use in the treatment of androgen-dependent disorders of the pilosebaceous unit or in the topical treatment of squamous cell carcinoma, or in the preparation of a medicament for use in the treatment of androgen-dependent disorders of the pilosebaceous unit or in the topical treatment of squamous cell carcinoma.
10. A method for the prophylactic or curative treatment of illnesses responsive to steroid sulfatase inhibition which comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 5 in free form or pharmaceutically acceptable salt form to a subject in need of such treatment.

INTERNATIONAL SEARCH REPORT

Application No
PCT/EP 99/02349

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D311/22 C07D335/06 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages.	Relevant to claim No.
A	WO 97 32872 A (IMPERIAL COLLEGE OF SCIENCE) 12 September 1997 (1997-09-12) page 1 - page 13; figures 7-9	1,6-9

☐

Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

20 August 1999

Date of mailing of the international search report

26/08/1999

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/ 02349

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Application No

PCT/EP 99/02349

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9732872 A	12-09-1997	AU 2225597 A EP 0885211 A	22-09-1997 23-12-1998

Form PCT/ISA/210 (patent family annex) (July 1992)